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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,161	01/19/2006	Pnina Fishman	FISHMAN19A	7305
1444 7590 01/25/2008 BROWDY AND NEIMARK, P.L.L.C. 624 NINTH STREET, NW SUITE 300 WASHINGTON, DC 20001-5303			EXAMINER HENRY, MICHAEL C	
			ART UNIT 1623	PAPER NUMBER
			MAIL DATE 01/25/2008	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/565,161	Applicant(s) FISHMAN ET AL.	
	Examiner Michael C. Henry	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>04/23/07</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claims 1-21 are pending in application

Information Disclosure Statement

The information disclosure statement filed complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Objections

Claim 10 is objected to because of the following informalities: The claim recites the phrase "A method according to claim 10" which appears to be a typographical error, since a claim cannot depend on itself. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the instant method of treating specific types of inflammatory condition or diseases such as arthritis or rheumatoid arthritis in a subject, does not reasonably provide enablement for treating all types or any type of inflammatory diseases or conditions, as encompassed by the claims, by administering a given composition or compound(s).

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without *undue experimentation*. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of treating a subject having an inflammatory condition, comprising administering to the subject a combination of an effective amount of methotrexate (MTX) and an effective amount of an agonist of the A3 adenosine receptor (A3AR agonist).

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims reads on treating all or any of the numerous inflammatory conditions or diseases as recited in claims 1, 12 and 13 herein.

Regarding the *Wands* factor (4) the predictability or unpredictability of the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly

unpredictable since one skilled in the art would recognize that the recitation encompasses all or any of the vast number of inflammatory diseases or conditions which include arthritis, pulmonary diseases, psoriasis, colitis, multiple sclerosis, systematic lupus erythematosus, juvenile diabetes, atherosclerosis, hypothyroidism, tonsillitis, pharyngitis, otitis media, pharyngitis, inflammatory bowel disease, bronchitis, inflammatory diseases of the central nervous system such as algal disorders, bacterial disorders, idiopathic inflammatory disorders, parasitic encephalomyelitis and viral disorders, which are known to involve various, many possible, different, separate and independent, even unknown pathology, etiologies, or symptoms. The treatment some of inflammatory diseases may require more than one distinct, separate, and independent methods, and regimens. For example, Pelvic inflammatory disease is often caused by a combination of different types of bacteria, so a combination (regimen) of medications is used to treat the infection or disease.

The skilled artisan would view the treating of all or any of the vast number of inflammatory diseases, by administering the VERY same compound, as being **highly unpredictable**.

In regard to these *Wands* factors, (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary:

In the instant case, no working examples are presented in the specification as filed showing how to treat inflammatory conditions or diseases other than arthritis or rheumatoid arthritis, i.e., no testing results provided for inflammatory conditions or diseases other than arthritis or rheumatoid arthritis.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad treatment of all or any inflammatory disease encompassed by the instant claims. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the embodiments of treating all or any inflammatory diseases recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 9, 10, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the instant method of treating specific types of autoimmune disease such as arthritis and rheumatoid arthritis in a subject, does not reasonably provide enablement for treating all types or any type of autoimmune diseases, as encompassed by the claims, by administering a given composition or compound(s).

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of treating an autoimmune condition or disease in a subject in need thereof, comprising administering to the subject an effective amount of the said composition or compound(s).

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims reads on treating all or any of the numerous autoimmune diseases recited in claims 9, 10, 20 and 21 herein.

Regarding the *Wands* factor (4) the predictability or unpredictability of the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that the recitation encompasses all or any of the autoimmune disease such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, scleroderma, pernicious anemia, myasthenia gravis, and Hashimoto's disease, which are known to involve various, many possible, different, separate and independent, even unknown pathology, etiologies, or symptoms. The method for the treatment of an autoimmune disease is not one but at least two distinct, separate, and independent methods. For example, as

defined by Ninham et al. (WO 85/05031, PTO-892), the immune response in a human or animal subject can be suppression or enhancement (see page 1-2). Autoimmune diseases can be treated by artificial suppression (immunosuppression) or enhancement (immunopotential), wherein these two treatments are involved in distinct and separate agents, processes and mechanisms, and most importantly which are in both opposite directions.

“To date, immunosuppressive drugs that have been developed to manipulate the immune response, are usually compounds of complex structure that have been discovered by accident. Further, their mode of action is often unknown or very unpredictable and administration of drugs can be accompanied by undersirable side-effects” (emphasis added). See page 2, in particular line 19-25.

The skilled artisan would view that the treating any autoimmune diseases, encompassing both suppression (immunosuppression) and enhancement (immunopotential), by administering the VERY same compound, as being **highly unpredictable**. Therefore, the skilled artisan would view that the treatment of all autoimmune diseases herein, by administering the same compound herein, is highly *unpredictable*.

In regard to these *Wands* factors, (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary: In the instant case, no working examples are presented in the specification as filed showing how to treat autoimmune disease other than arthritis or rheumatoid arthritis, i.e., no testing results provided.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad treatment of all or any autoimmune disease encompassed by the instant claims. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the embodiments of treating all or any autoimmune diseases recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jeurissen et al. (Arthritis and rheumatism, 1991 Aug) Vol. 34, No. 8, pages 961-972) in view of et al. Fishman (US 2004/0167094 A1).

In claim 1, applicant claims a method of treating a subject having an inflammatory condition, comprising administering to the subject a combination of an effective amount of methotrexate (MTX) and an effective amount of an agonist of the A3 adenosine receptor (A3AR agonist). Claims 2-11 are drawn said method, wherein the A3AR agonist is administered to specific time per day, specific daily dosages, administered orally, the specific agonist are used and specific inflammatory condition (rheumatoid arthritis) is treated

Jeurissen et al. disclose a method of treating a subject having an inflammatory condition (rheumatoid arthritis), comprising administering to the subject a combination of an effective amount of methotrexate (MTX) (see abstract).

The difference between applicant's claimed method and the method taught by Jeurissen et al. is that the applicant also uses an agonist of the A3 adenosine receptor (A3AR agonist) in their composition in addition to the methotrexate (MTX).

Fishman discloses a method of treating inflammatory arthritis (rheumatoid arthritis), by administering to a subject an agonist of the A3 adenosine receptor (A3AR agonist) N6-(3-iodobenzyl)-adenosine 5'-N-methyl-uronamide (IB-MECA) and 2-chloro-N6-(3-iodobenzyl)-adenosine-5'-N-methyl-uronamide (CL-IB-MECA) (see abstract).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, in view of Jeurissen et al and Fishman, to treat rheumatoid arthritis in a subject by administering to said subject a composition comprising a combination of methotrexate and an A3AR agonist such as IB-MECA or CL-IB-MECA, since the combination of compounds that are used to treat the same diseases are well known in the art. More specifically,

it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose. In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

One having ordinary skill in the art would have been motivated in view of Jeurissen et al and Fishman, to treat rheumatoid arthritis in a subject by administering to said subject a composition comprising a combination of methotrexate and an A3AR agonist such as IB-MECA or CL-IB-MECA, because a skilled artisan would reasonably be expected to prepare composition comprising a combination of the compounds taught by Jeurissen et al and Fishman., to treat rheumatoid arthritis based on factors such as type and/or severity of the rheumatoid arthritis. It should be noted that the use of different schedules administrations or dosages are common in the art and is well within the purview of a skilled artisan and depends on factors such as the severity or type of the rheumatoid arthrithis and the weight, age and type of the subject treated.

Claim 13 is drawn to a method of treating a subject having an inflammatory condition and indicated for treatment with an A3AR agonist, comprising administering to the subject an effective amount of an of MTX , wherein MTX is administered to the subject once weekly.

Jeurissen et al. disclose a method of treating a subject having an inflammatory condition (rheumatoid arthritis), comprising administering to the subject a combination of an effective amount of methotrexate (MTX) (see abstract).

The difference between applicant's claimed method and the method taught by Jeurissen et al. is that Jeurissen et al. do not disclose that the said subject is indicated for treatment with an A3AR agonist.

Fishman discloses a method of treating inflammatory arthritis (rheumatoid arthritis), by administering to a subject an agonist of the A3 adenosine receptor (A3AR agonist) N6-(3-iodobenzyl)-adenosine 5'-N-methyl-uronamide (IB-MECA) and 2-chloro-N6-(3-iodobenzyl)-adenosine-5'-N-methyl-uronamide (CL-IB-MECA) (see abstract).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, in view of Jeurissen et al. and Fishman, to treat rheumatoid arthritis in a subject by administering to the said subject an MTX, regardless of whether the subject is indicated for treatment with A3AR agonist such as IB-MECA or CL-IB-MECA and especially since Fishman discloses that A3AR agonist such as IB-MECA or CL-IB-MECA can be used to treat inflammatory condition (rheumatoid arthritis), and since the administration of different drugs or compounds to treat the same condition in the same patient is common in the art and is well within the purview.

One having ordinary skill in the art would have been motivated in view of Jeurissen et al. and Fishman, to treat rheumatoid arthritis in a subject by administering to the said subject an MTX, regardless of whether the subject is indicated for treatment with A3AR agonist such as IB-MECA or CL-IB-MECA, because a skilled artisan would reasonably be expected use or administer additional compounds such MTX, to treat rheumatoid arthritis (the same condition or disease) based on factors such as type and/or severity of the rheumatoid arthritis. It should be

noted that the use of different schedules administrations or dosages are common in the art and is well within the purview of a skilled artisan and depends on factors such as the severity or type of the rheumatoid arthrithis and the weight, age and type of the subject treated. It should be noted that the administration of different drugs or compounds to treat the same condition in the same patient is common in the art and is well within the purview of a skilled artisan and depends on factors such as the severity or type of the rheumatoid arthrithis and the weight, age and type of the subject treated.

Claims 12, 14-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman (US 2004/0167094 A1) in view of Jeurissen et al. (Arthritis and rheumatism, 1991 Aug) Vol. 34, No. 8, pages 961-972).

In claim 12, applicant claims a method of treating a subject having an inflammatory condition and treated with MTX, comprising administering to the subject an effective amount of an A3AR agonist. Claims 14-21 are drawn said method, wherein the A3AR agonist is administered to specific time per day, specific daily dosages, administered orally, the specific agonist are used and specific inflammatory condition (rheumatoid arthritis) is treated.

Fishman discloses a method of treating inflammatory arthritis (rheumatoid arthritis), by administering to a subject an agonist of the A3 adenosine receptor (A3AR agonist) N6-(3-iodobenzyl)-adenosine 5'-N-methyl-uronamide (IB-MECA) and 2-chloro-N6-(3-iodobenzyl)-adenosine-5'-N-methyl-uronamide (CL-IB-MECA) (see abstract).

The difference between applicant's claimed method and the method taught by Fishman is that Fishman does not disclose that the said subject that is treated with the A3AR agonist is also being treated with methotrexate (MTX).

Jeurissen et al. disclose a method of treating a subject having an inflammatory condition (rheumatoid arthritis), comprising administering to the subject a combination of an effective amount of methotrexate (MTX) (see abstract).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, in view of Fishman and Jeurissen et al., to treat rheumatoid arthritis in a subject by administering to the said subject an A3AR agonist such as IB-MECA or CL-IB-MECA, regardless of whether the subject is being treated with MTX and especially since Jeurissen et al. disclose that methotrexate (MTX) can be used to treat inflammatory condition (rheumatoid arthritis), and since the administration of different drugs or compounds to treat the same condition in the same patient is common in the art and is well within the purview.

One having ordinary skill in the art would have been motivated in view of Fishman and Jeurissen et al., to treat rheumatoid arthritis in a subject by administering to the said subject an A3AR agonist such as IB-MECA or CL-IB-MECA, regardless of whether the subject is being treated with MTX, because a skilled artisan would reasonably be expected additional compounds such Fishman's A3AR agonist, to treat rheumatoid arthritis (the same condition or disease) based on factors such as type and/or severity of the rheumatoid arthritis. It should be noted that the use of different schedules administrations or dosages are common in the art and is well within the purview of a skilled artisan and depends on factors such as the severity or type of the

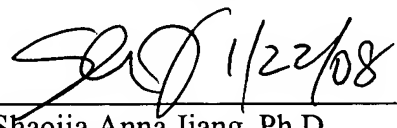
rheumatoid arthritis and the weight, age and type of the subject treated. It should be noted that the administration of different drugs or compounds to treat the same condition in the same patient is common in the art and is well within the purview of a skilled artisan and depends on factors such as the severity or type of the rheumatoid arthritis and the weight, age and type of the subject treated.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry



Shaojia Anna Jiang, Ph.D.
Supervisory Patent Examiner
Art Unit 1623

January 20, 2008.